HETEROCYCLES, Vol. 89, No. 2, 2014, pp. 413 - 425. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 25th November, 2013, Accepted, 18th December, 2013, Published online, 6th January, 2014
DOI: 10.3987/COM-13-12899

STUDIES ON THE CHEMICAL TRANSFORMATIONS OF SIMPLE CONDENSATES DERIVED FROM 3-FORMYLCHROMONE UNDER NUCLEOPHILIC CONDITIONS

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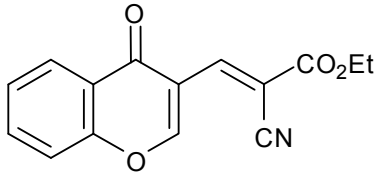
Abstract – The chemical reactivity of the simple condensates **1** and **2**, derived from 3-formylchromone, was studied towards some nucleophilic reactions. Reactions of compounds **1** and **2** with some nucleophilic reagents mainly proceed *via* nucleophilic addition at the exocyclic vinyl bond followed by either elimination or cyclization during the course of reactions. A variety of products were obtained depending on the substrate and the nucleophile used.

INTRODUCTION

Chromone derivatives have attracted attention from the point of view of both biological activity,[1-3] and organic synthesis.[4-6] The chemical reactivity of 3-substituted chromones towards nucleophilic reagents is widely different depending on the nature of the substituents at the 3-position and the reaction conditions. Several reports describe the action of different nucleophiles on various 3-substituted chromones, and a variety of heterocyclic systems were obtained.[7-15] In continuation to our interest in the area of 3-substituted chromones,[12-19] the present work aimed to study the chemical behavior of the simple condensates **1** and **2** (Figure 1) towards a variety of nitrogen and carbon nucleophiles.



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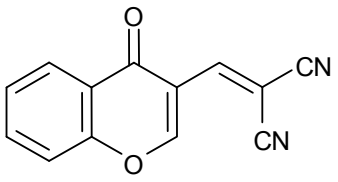


2

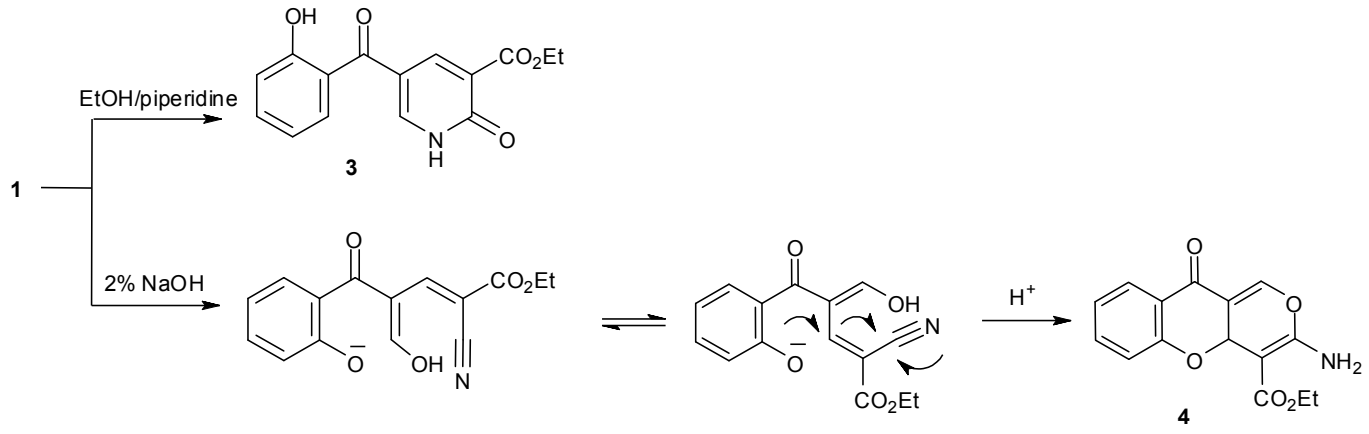
Figure 1

RESULTS AND DISCUSSION

The simple condensates **1** and **2**, derived from condensation reaction of 3-formylchromone with ethyl cyanoacetate and malononitrile, respectively (Figure 1), may be of interest in the synthesis of various heterocyclic systems due to the availability of diverse electron deficient sites. The present work aimed to study the effect of a variety of bifunctional nitrogen and carbon nucleophiles on the simple condensation products **1** and **2**.

3-Substituted chromones underwent different transformations upon treatment with simple nucleophilic reagents.[9,12,13] Thus, boiling ethyl ester **1** in 95% ethanol containing one drop of piperidine afforded the pyridine derivative **3** *via* partial hydrolysis of the cyano group in compound **1** to amide function which underwent intramolecular nucleophilic attack at the C-2 position of chromone moiety with concomitant γ-pyrone ring opening to afford the target compound **3** (Scheme 1).[17]

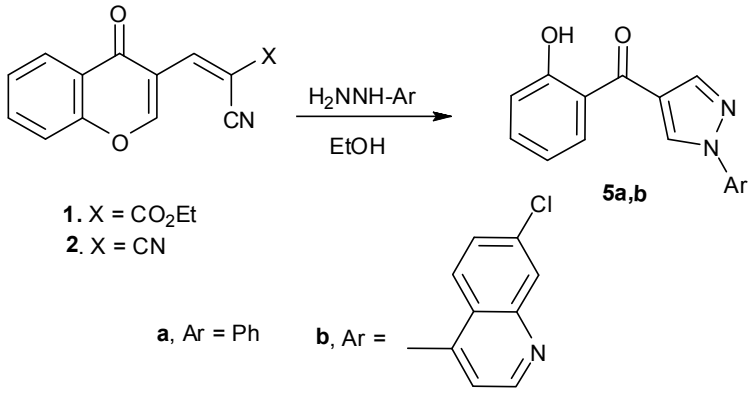
On the other hand, treatment of compound **1** with aqueous 2% NaOH solution at 70 °C resulted in ring transformation to produce ethyl 3-amino-10-oxo-4a*H*,10*H*-pyrano[4,3-*b*]chromene-4-carboxylate (**4**) as shown in Scheme 1. The ^{1}H NMR spectrum of compound **4** revealed the presence of two characteristic singlet signals at δ 5.89 and 8.14 ppm attributed to the H-4a and H-1, respectively, in addition to a triplet and quartet signals at δ 1.40 and 4.52 ppm assigned to the ethoxycarbonyl protons.



Scheme 1

The chemical reactivity of ethyl ester **1** was studied towards some hydrazine derivatives. Thus, refluxing compound **1** with phenylhydrazine in absolute ethanol afforded the pyrazole derivative **5a**, *via* nucleophilic addition at the exocyclic vinyl bond with elimination of ethyl cyanoacetate followed by nucleophilic attack of the NH group at C-2 position with concomitant γ-pyrone ring opening (Scheme 2). Structure of compound **5a** was found to be identical with that previously obtained from the condensation of 3-formylchromone with phenylhydrazine as earlier published.[21,22] Similarly, condensation of compound **1** with 7-chloro-4-hydrazinoquinoline in absolute ethanol gave the quinolinylpyrazole

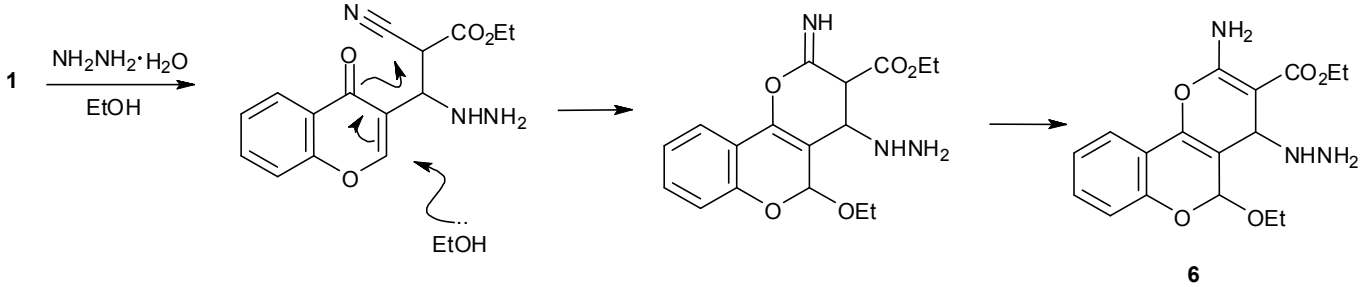
derivative **5b** (Scheme 2). The IR and ^{1}H NMR spectra showed the disappearance of the cyano and ethoxycarbonyl groups which confirm the elimination of ethyl cyanoacetate during the course of the reaction.



Scheme 2

The same products **5a,b** were obtained from reaction of compound **2** with phenylhydrazine and 7-chloro-4-hydrazinoquinoline, respectively, under the same reaction conditions (Scheme 2).

Out of the ordinary, hydrazine hydrate showed different behavior when reacted with ethyl ester **1**. Refluxing compound **1** with hydrazine hydrate in absolute ethanol afforded a yellow crystalline product after 5 min (70% yield) which was identified as ethyl 2-amino-5-ethoxy-4-hydrazinyl-4*H*,5*H*-pyrano-[3,2-*c*]chromene-3-carboxylate (**6**), the proposed mechanism for the formation of compound **6** is depicted in Scheme 3. The ^{1}H NMR spectrum showed characteristic singlet signal at δ 6.35 ppm assigned to H-5 (as O-CH-O), in addition to characteristic doublet, exchanged singlet in D_2O, at δ 5.85 ppm attributed to the H-4 proton.

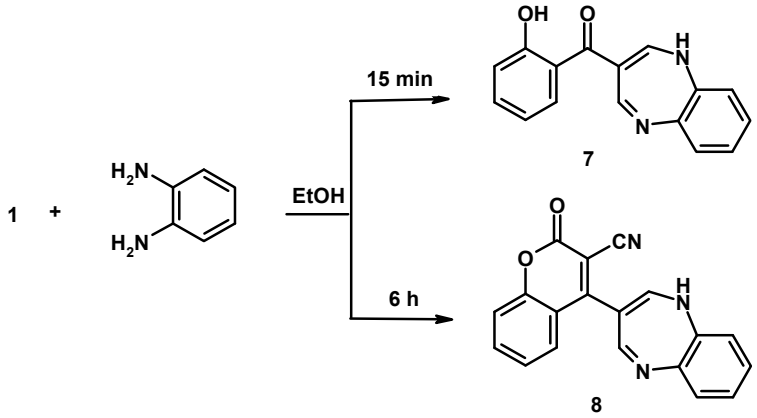


Scheme 3

On the other hand, the ring transformation of ethyl ester **1** was studied towards some 1,4-bifunctional nucleophiles. Thus, treatment of compound **1** with *o*-phenylenediamine in absolute ethanol afforded the benzodiazepine derivative **7** *via* nucleophilic addition at exocyclic vinyl carbon followed by elimination of ethyl cyanoacetate with concomitant intramolecular nucleophilic attack of the other amino group at

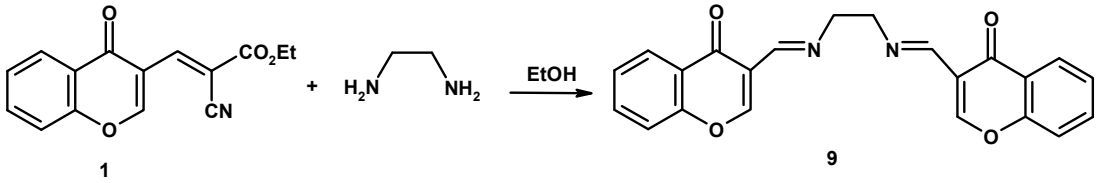
C-2 position with γ-pyrone ring opening (Scheme 4). The IR and ^{1}H NMR spectra of compound **7** revealed the absence of the nitrile and ethoxycarbonyl functions. ^{13}C NMR spectrum of compound **7** showed characteristic signal assigned to C-$3_{benzodiazepine}$ at δ 88.2. Further, the mass spectrum of compound **7** showed the molecular ion peak at m/e 264 corresponding to the formula weight (264.29) and supports the identify of structure.

In another experiment, refluxing compound **1** with *o*-phenylenediamine for 6 h afforded 4-(1*H*-1,5-benzodiazepin-3-yl)coumarin-3-carbonitrile (**8**) (Scheme 4). In this reaction we found that the yellow crystalline product which formed after 15 min. was dissolved during the reaction and a new product **8** was obtained. Compound **8** obtained *via* the formation of benzodiazepine **7** which then reacted with ethyl cyanoacetate. The IR spectrum of compound **8** showed characteristic absorption band at 2222 cm^{-1} attributed to the nitile function. The ^{1}H NMR spectrum of compound **8** showed the disappearance of OH proton which was appeared at δ 14.29 ppm in the ^{1}H NMR spectrum of compound **7**.



Scheme 4

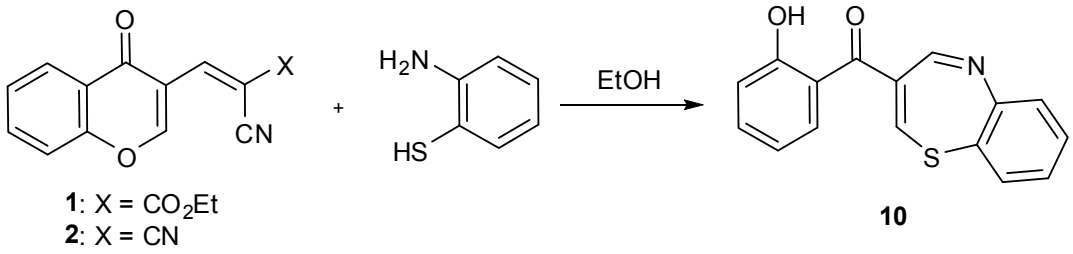
On the other hand, ethylenediamine showed different behavior and usually reacted with two equivalents of compound **1** to produce 1,2-*bis*[(chromon-3-yl)methyleneamino]ethane (**9**) (Scheme 5).[23] The ^{1}H NMR spectrum of compound **9** showed three characteristic singlet signals at δ 3.69, 8.02 and 8.17 ppm attributed to CH_2, CH=N and H-2, respectively.



Scheme 5

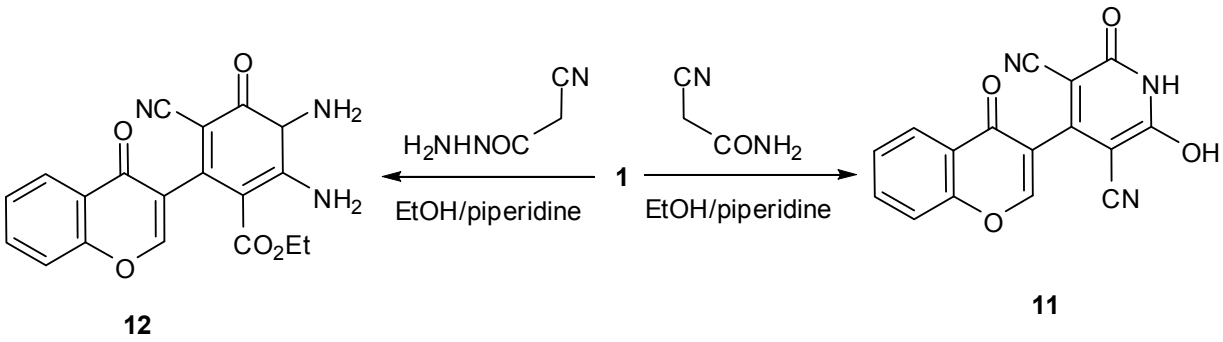
2-Aminothiophenol behaves similarly to *o*-phenylenediamine and produced the benzothiazepine derivative **10** when reacted with ethyl ester **1**. Herein, we found that the same product **10** was obtained

from the condensation reaction of compound **2** with 2-aminothiophenol under the same reaction conditions (the same mp, mmp and spectral data) (Scheme 6).



Scheme 6

The chemical reactivity of compound **1** towards some carbon nucleophiles was studied. Thus, treating compound **1** with cyanoacetamide and cyanoacetohydrazide, in absolute ethanol containing few drops of piperidine, afforded the pyridone derivatives **11** and **12**, respectively (Scheme 7).[24]

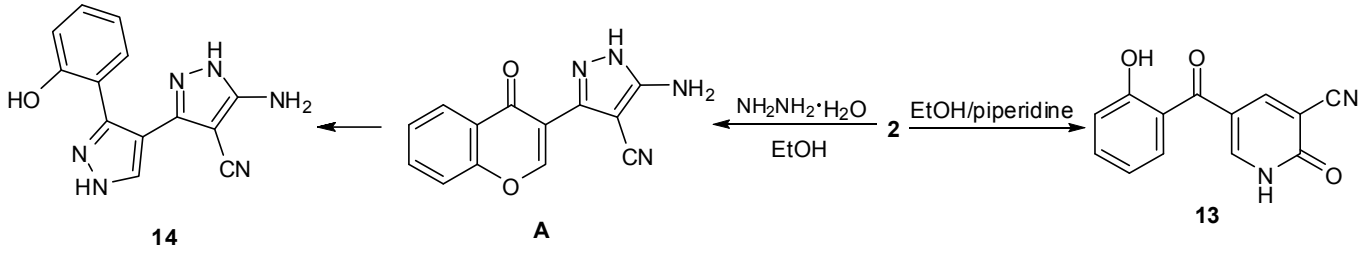


Scheme 7

Next, the chemical reactivity of compound **2** under nucleophilic conditions was studied. Thus, refluxing compound **2** in 95% ethanol containing one drop of piperidine afforded 5-(2-hydroxybenzoyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (**13**), *via* hydrolysis of one of the cyano groups to the amide group which underwent nucleophilic attack at C-2 position followed by γ-pyrone ring opening (Scheme 8).[25] The IR spectrum of compound **13** showed characteristic absorption bands at 1688 and 1641 cm^{-1} assigned to the $C{=}O_{cyclic\ amide}$ and $C{=}O_{benzoyl}$ groups. The ^1H NMR spectrum of compound **13** showed characteristic singlet signals at δ 8.05 and 8.42 ppm attributed to H-4 and H-6 of the pyridine nucleus, in addition to two exchangeable signals at δ 10.33 and 13.10 ppm attributed to NH and OH protons, respectively.

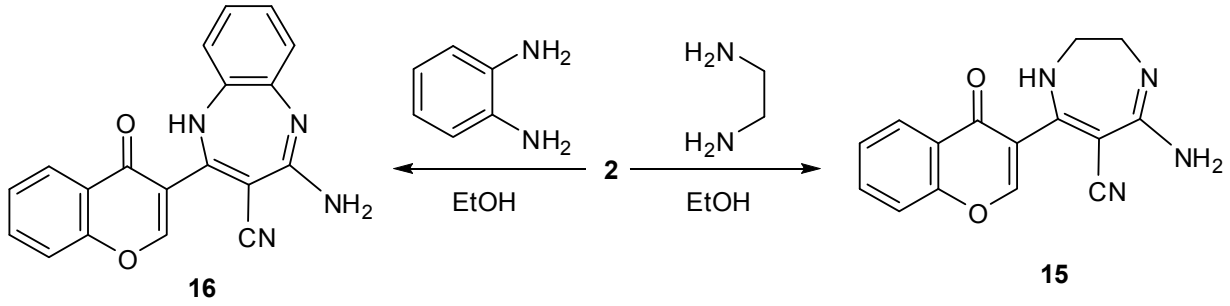
Ring transformation of compound **2** was achieved by hydrazine hydrate to produce the pyrazolylpyrazole derivative **14** as shown Scheme 8. The reaction proceeds *via* the formation of pyrazole intermediate **A** followed by nucleophilic attack of another molecule of hydrazine hydrate at C-2 position with γ-pyrone ring opening followed by cyclocondensation to afford the pyrazolylpyrazole derivative **14**. The IR

spectrum of compound **14** showed characteristic absorption band at 2221 cm^{-1} due to the nitrile function (C≡N). Its ^{1}H NMR spectrum showed characteristic singlet at δ 7.64 ppm assigned to H-$5_{pyrazole}$.



Scheme 8

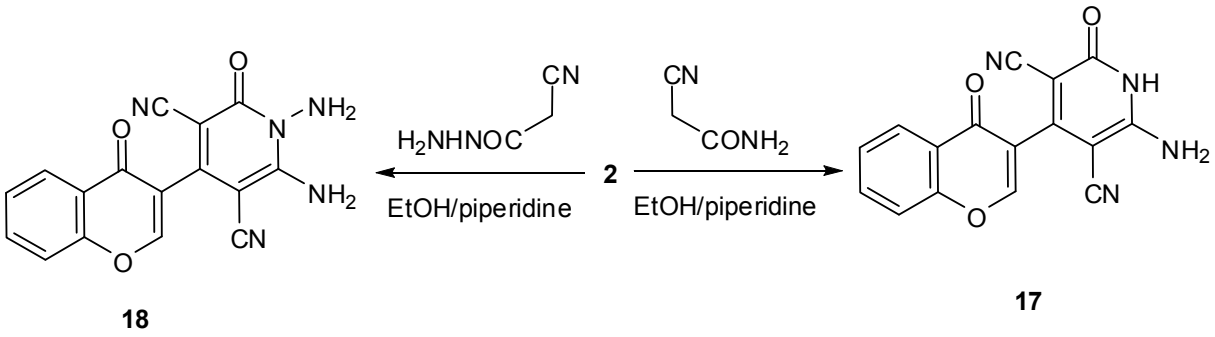
Reaction of compound **2** with ethylenediamine and *o*-phenylenediamine in absolute ethanol afforded diazepine **15** and benzodiazepine **16**, respectively, *via* nucleophilic addition of one amino group at exocyclic vinyl carbon followed by cycloaddition of the other amino group onto the nitrile function with concomitant dehydrogenation (Scheme 9). The IR spectrum of compound **15** showed characteristic absorption bands at 3324 (NH_2, NH), 2212 (C≡N) and 1645 cm^{-1} (C=$O_{\gamma\text{-pyrone}}$). Its ^{1}H NMR spectrum showed two characteristic singlet signals at δ 3.83 ($2CH_2$) and 8.88 ppm (H-$2_{chromone}$). The ^{1}H NMR spectrum of compound **16** showed characteristic singlet at δ 8.75 ppm assigned to H-2 of chromone moiety. ^{13}C NMR spectrum of compound **16** showed characteristic signals attributed to C-$3_{benzodiazepine}$ and C≡N at δ 71.5 and 116.2, respectively. The mass spectrum of compound **16** showed the molecular ion peak at *m/e* 328 corresponding to the molecular formula ($C_{19}H_{12}N_4O_2$) and supports the structure.



Scheme 9

The chemical reactivity of compound **2** was studied towards some carbon nucleophiles. Thus, treating compound **2** with cyanoacetamide and cyanoacetohydrazide gave chromonylpyridine derivatives **17** and **18**, respectively (Scheme 10). The ^{1}H NMR spectra of compounds **17** and **18** showed characteristic singlets assigned to the H-$2_{chromone}$ at 9.26 and 9.38 ppm, respectively. Further, the mass spectrum of compound **18** showed the molecular ion peak at *m/e* 319 corresponding to the formula weight (319.28)

and support the identify of structure.



Scheme 10

EXPERIMENTAL

Melting points are uncorrected and were determined on a digital Stuart SMP3 apparatus. Infrared spectra were measured on FTIR Nicolet IS10 spectrophotometer (cm^{-1}), using KBr disks. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured on Mercury-300BB, using DMSO-d_6 as a solvent and tetramethylsilane as an internal standard. Mass spectra were measured using GC-MS qp 1000 ex Shimadzu mass spectrometer instrument (70 eV). Elemental microanalyses were performed on a Perkin-Elmer CHN-2400 analyzer at the Chemical War Department, Ministry of Defense, Egypt. Ethyl 2-cyano-3-(4-oxo-4*H*-chromen-3-yl)prop-2-enoate (**1**)[21] and [(4-oxo-4*H*-chromen-3-yl)methylidene]-propanedinitrile (**2**)[26] were prepared according to the published methods.

Ethyl 5-(2-hydroxybenzoyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (3).

A mixture of compound **1** (0.54 g, 2 mmol) in 95% EtOH (15 mL) containing one drop of piperidine was heated under reflux for 30 min. The solid obtained after cooling was filtered off and crystallized from aqueous EtOH to give compound **3** as white crystals, yield (0.32 g, 59%), mp 176−177 °C (lit., mp 177 °C).[20] IR (KBr, cm^{-1}): 3579, 3502 (OH, NH), 3065 ($CH_{arom.}$), 2991, 2846, 2805 ($CH_{aliph.}$), 1720 ($C{=}O_{ester}$ and $C{=}O_{pyridone}$), 1628 ($C{=}O_{hydrogen\ bonded}$), 1601 (C=N), 1560 (C=C).

Ethyl 3-amino-10-oxo-4a*H*,10*H*-pyrano[4,3-*b*]chromene-4-carboxylate (4).

A mixture of compound **1** (0.54 g, 2 mmol) and aqueous sodium hydroxide solution (2%, 20 mL), was stirred at 70 °C for 2 h. After cooling, the reaction mixture was neutralized with dilute HCl. The precipitated solid was filtered off and crystallized from EtOH to give compound **4** as yellow crystals, yield (0.28 g, 52%), mp 211 °C. IR (KBr, cm^{-1}): 3422 (NH_2), 3065 ($CH_{arom.}$), 2978, 2933 ($CH_{aliph.}$), 1740 ($C{=}O_{ester}$), 1643 ($C{=}O_{\gamma\text{-pyrone}}$), 1608 (C=C). ^{1}H NMR (DMSO-d_6, δ): 1.40 (t, 3H, CH_3, J = 7.4 Hz), 4.06 (bs, 2H, NH_2 exchangeable with D_2O), 4.52 (q, 2H, CH_2, J = 7.0 Hz), 5.89 (s, 1H, H-4a), 6.99 (d, 1H, H-6, J = 7.6 Hz), 7.16 (t, 1H, H-8, J = 7.2 Hz), 7.51 (t, 1H, H-7, J = 7.8 Hz), 7.76 (d, 1H, H-9, J = 7.6 Hz),

8.14 (s, 1H, H-1). Anal. Calcd for $C_{15}H_{13}NO_5$ (287.27): C, 62.72; H, 4.56; N, 4.88%. Found: C, 62.54; H, 4.27; N, 4.60%.

4-(2-Hydroxybenzoyl)-1-phenyl-1*H*-pyrazole (5a).

A mixture of compound **1** or **2** (2 mmol) and phenylhydrazine (0.22 mL, 2 mmol), in absolute EtOH was heated under reflux for 1 h. The solid obtained after cooling was filtered off and recrystallized from MeOH to give compound **5a** as white crystals, yield (37−39%), mp 115 °C (lit., mp 115 °C,[21] 113 °C [22]).

4-(2-Hydroxybenzoyl)-1-(7-chloroquinolin-4-yl)-1*H*-pyrazole (5b).

A mixture of compound **1** or **2** (2 mmol) and 7-chloro-4-hydrazinoquinoline (0.38 g, 2 mmol) in absolute EtOH (25 mL) was heated under reflux 1 h. After cooling, the solid so formed was filtered off and crystallized from DMF/H_2O to give compound **5b** as white crystals, yield (51−54%), mp 291 °C. IR (KBr, cm^{-1}): 3301 (OH), 3060 ($CH_{arom.}$), 1628 (C=O), 1609 (C=N), 1594 (C=C). ^{1}H NMR (DMSO-d_6, δ): 6.90 (d, 1H, Ar-H), 6.96−7.05 (m, 1H, Ar-H), 7.51 (t, 1H, Ar-H, J = 7.5 Hz), 7.76−7.80 (m, 1H, Ar-H), 7.88 (d, 1H, Ar-H), 8.18 (s, 1H, H-$8_{quinoline}$), 8.25 (d, 1H, Ar-H), 8.41 (s, 1H, H-$5_{pyrazole}$), 8.52 (d, 1H, H-$3_{quinoline}$), 9.04 (s, 1H, H-$3_{pyrazole}$), 9.10 (d, 1H, H-$2_{quinoline}$), 11.06 (bs, 1H, OH exchangeable with D_2O). Anal. Calcd for $C_{19}H_{12}N_3O_2Cl$ (349.78): C, 65.24; H, 3.46; N, 12.01%. Found: C, 65.28; H, 3.28; N, 11.54%.

Ethyl 2-amino-5-ethoxy-4-hydrazinyl-4*H*,5*H*-pyrano[3,2-*c*]chromene-3-carboxylate (6).

A mixture of compound **1** (0.54 g, 2 mmol) and hydrazine hydrate (0.1 mL, 2 mmol) in absolute EtOH (25 mL) was heated under reflux for 5 min. The solid obtained during heating was filtered off and crystallized from DMF/EtOH to give compound **6** as yellow crystals, yield (0.38 g, 70%), mp 241 °C. IR (KBr, cm^{-1}): 3410, 3241, 3283, 3215 ($2NH_2$, NH), 2978, 2905 ($CH_{aliph.}$), 1663 ($C{=}O_{ester}$), 1615 (C=C). ^{1}H NMR (DMSO-d_6, δ): 1.11 (t, 3H, CH_3, J = 7.2 Hz), 1.24 (t, 3H, CH_3, J = 7.2 Hz), 4.05 (q, 2H, CH_2, J = 7.2 Hz), 4.11 (q, 2H, CH_2, J = 7.8 Hz), 5.23 (s, 1H, NH exchangeable with D_2O), 5.85 (d, 1H, H-4 exchanged to singlet with D_2O, J = 8.4 Hz), 6.35 (s, 1H, H-5 as O-CH-O), 6.40 (d, 1H, NH exchangeable with D_2O), 6.89 (t, 1H, H-8, J = 8.4 Hz), 7.13 (t, 1H, H-7), 7.29 (t, 1H, H-9), 7.79 (d, 1H, H-10), 8.84 (bs, 2H, NH_2 exchangeable with D_2O), 9.84 (bs, 1H, NH exchangeable with D_2O). M/z (*I* %): 301 (M-EtOH, 10), 286 (58), 239 (11), 224 (10), 196 (10), 166 (100), 147 (22), 121 (72), 120 (66), 94 (52), 77 (10), 65 (54). Anal. Calcd for $C_{17}H_{21}N_3O_5$ (347.37): C, 58.78; H, 6.09; N, 12.10%. Found: C, 58.95; H, 6.31; N, 12.18%.

3-(2-Hydroxybenzoyl)-1*H*-1,5-benzodiazepine (7).

A mixture of compound **1** (0.54 g, 2 mmol) and *o*-phenylendiamine (0.22 g, 2 mmol) in absolute EtOH (30 mL) was heated under reflux for 15 min. The yellow crystals obtained during heating was filtered off and crystallized from EtOH to give compound **7** as yellow crystals, yield (0.44 g, 82%), mp 220 °C. IR (KBr, cm^{-1}): 3090 (NH), 1637 (C=O), 1611 (C=N), 1570 (C=C). ^{1}H NMR (DMSO-d_6, δ): 6.92−6.98 (m, 3H, Ar-H), 7.16−7.19 (m, 1H, Ar-H), 7.31−7.40 (m, 4H, Ar-H), 8.56 (d, 2H, H-$2_{diazepine}$ and H-$4_{diazepine}$),

10.19 (s, 1H, NH exchangeable with D_2O), 14.29 (s, 1H, OH exchangeable with D_2O). ^{13}C NMR (DMSO-d_6, δ): 88.2, 117.3, 120.0, 121.7, 122.2, 123.0, 123.9, 126.9, 133.1, 133.8, 134.8, 136.4, 139.5, 152.8, 155.2, 159.6. M/z (*I* %): 264 (16), 210 (14), 206 (27), 185 (14), 131 (22), 108 (38), 91 (24), 77 (24), 65 (27), 60 (100). Anal. Calcd for $C_{16}H_{12}N_2O_2$ (264.29): C, 72.72; H, 4.58; N, 10.60%. Found: C, 72.50; H, 4.65; N, 10.84%.

4-(1*H*-1,5-Benzodiazepin-3-yl)-coumarin-3-carbonitrile (8).

A mixture of compound **1** (0.54 g, 2 mmol) and *o*-phenylendiamine (0.22 g, 2 mmol) in absolute EtOH (30 mL) was heated under reflux for 6 h. The solid obtained after cooling was filtered off and crystallized from DMF to give compound **8** as yellow crystals, yield (0.24 g, 45%), mp > 300 °C. IR (KBr, cm^{-1}): 3133 (NH), 2222 (C≡N), 1663 (C=O), 1623 (C=N), 1592 (C=C). ^1H NMR (DMSO-d_6, δ): 6.80−7.20 (m, 2H, Ar-H), 7.35−7.55 (m, 4H, Ar-H), 7.78−7.92 (m, 2H, Ar-H), 8.60 (bs, 2H, Ar-H). M/z (*I* %): 312 (M-1, 21), 311 (M-2, 32), 188 (32), 138 (26), 121 (47), 93 (37), 57 (100). Anal. Calcd for $C_{19}H_{11}N_3O_2$ (313.32): C, 72.81; H, 3.54; N, 13.41%. Found: C, 72.73; H, 3.41; N, 13.08%.

1,2-*Bis*[(chromon-3-yl)methyleneamino]ethane (9).

A mixture of compound **1** (0.54 g, 2 mmol) and ethylenediamine (0.12 mL, 2 mmol) in absolute EtOH (20 mL) was heated under reflux for 2 h. After cooling, the resulting precipitate was filtered off and crystallized from DMF to give compound **9** as yellow crystals, yield (0.41 g, 55%), mp 200−201 °C (lit., mp 200 ºC).[23] IR (KBr, cm^{-1}): 3067 ($CH_{arom.}$), 2931, 2861 ($CH_{aliph.}$), 1679 (C=O), 1610 (C=N), 1604 (C=C). ^1H NMR (DMSO-d_6, δ): 3.69 (s, 4H, $2CH_2$), 6.69−6.92 (m, 4H, Ar-H), 7.28−7.50 (m, 4H, Ar-H), 8.02 (s, 2H, 2CH=N), 8.17 (s, 2H, H-$2_{chromone}$).

3-(2-Hydroxybenzoyl)-1,5-benzothiazepine (10).

A mixture of compound **1** or **2** (2 mmol) and 2-aminothiophenol (0.26 g, 2 mmol) in absolute EtOH (20 mL) was heated under reflux for 3 h. After cooling, the pale yellow precipitate was filtered off and crystallized from EtOH to give compound **10** as pale yellow crystals, yield (32−34%), mp 145 °C. IR (KBr, cm^{-1}): 3057 ($CH_{arom.}$), 1622 ($C{=}O_{hydrogen\ bonded}$), 1589 (C=N), 1558 (C=C). ^{1}HNMR (DMSO-d_6, δ): 6.99−7.10 (m, 3H, Ar-H), 7.39−7.44 (m, 3H, Ar-H), 7.54 (t, 1H, Ar-H), 8.06 (d, 1H, Ar-H), 8.17−8.19 (m, 2H, Ar-H), 11.58 (s, 1H, OH, exchangeable with D_2O). Anal. Calcd for $C_{16}H_{11}NO_2S$ (281.34): C, 68.31; H, 3.94; N, 4.98; S, 11.40%. Found: C, 68.15; H, 3.63; N, 4.80; S, 11.21%.

6-Hydroxy-2-oxo-4-(4-oxo-4*H*-chromen-3-yl)-1,2-dihydropyridine-3,5-dicarbonitrile (11).

A mixture of compound **1** (0.54 g, 2 mmol) and cyanoacetamide (0.17 g, 2 mmol) in absolute EtOH (30 mL) containing two drops of piperidine was heated under reflux for 3 h. The formed precipitate during heating was filtered off and crystallized from DMF/H_2O to give compound **11** as yellow crystals, yield (0.21 g, 34%), mp 212 °C. IR (KBr, cm^{-1}): 3408 (OH), 3188 (NH), 3025 ($CH_{arom.}$), 2271, 2228 (2 C≡N), 1686 ($C{=}O_{pyridone}$), 1630 ($C{=}O_{\gamma\text{-pyrone}}$), 1617 (C=C). ^1H NMR (DMSO-d_6, *δ*): 6.92 (t, 1H, H-$6_{chromone}$, *J* =

7.6 Hz), 7.32 (d, 1H, H-$8_{chromone}$, J = 6.8 Hz), 7.40 (t, 1H, H-$7_{chromone}$, J = 6.8 Hz), 7.62 (d, 1H, H-$5_{chromone}$), 8.02 (s, 1H, NH), 8.37 (s, 1H, H-$2_{chromone}$), 10.31 (s, 1H, OH exchangeable with D_2O). M/z (*I* %): 305 (M^+, 4), 289 (5), 265 (6), 240 (46), 222 (8), 194 (11), 147 (14), 120 (100), 105 (7), 92 (39), 80 (86), 77 (11), 64 (77). Anal. Calcd for $C_{16}H_7N_3O_4$ (305.25): C, 62.96; H, 2.31; N, 13.77%. Found: C, 62.75; H, 2.24; N, 13.54%.

Ethyl 1,2-diamino-5-cyano-6-oxo-4-(4-oxo-4*H*-chromen-3-yl)-1,6-dihydropyridine-3-carboxylate (12).

A mixture of compound **1** (0.54 g, 2 mmol) and cyanoacetohydrazide (0.2 g, 2 mmol), in absolute EtOH (30 mL) containing two drops of piperidine, was heated under reflux for 30 min. The pale yellow precipitate obtained during heating was filtered off and crystallized from EtOH to give compound **12** as white crystals, yield (0.26 g, 48%), mp 195 °C. IR (KBr, cm^{-1}): 3280 ($2NH_2$), 3060 ($CH_{arom.}$), 2983, 2920 ($CH_{aliph.}$), 2263 (C≡N), 1720 ($C=O_{ester}$), 1680 ($C=O_{pyridone}$), 1625 ($C=O_{\gamma\text{-pyrone}}$), 1605 (C=C). ^{1}HNMR (DMSO-d_6, δ): 1.35 (t, 3H, CH_3, J = 7.5 Hz), 4.44 (q, 2H, CH_2, J = 7.5 Hz), 4.56 (s, 2H, NH_2 exchangeable with D_2O), 6.97-7.04 (m, 2H, Ar-H), 7.49−7.53 (m, 2H, Ar-H), 8.49 (s, 1H, 1H of *C*-NH_2 exchangeable with D_2O), 9.43 (s, 1H, H-$2_{chromone}$), 10.48 (s, 1H, 1H of *C*-NH_2 exchangeable with D_2O). ^{13}C NMR (DMSO-d_6, δ): 14.1, 61.7, 95.6, 114.0, 116.1, 116.5, 119.5, 123.7, 124.4, 130.8, 133.4, 134.2, 135.8, 149.9, 156.8, 160.7, 162.3, 192.0. M/z (*I* %): 350 (M-NH_2, 97), 321 (100), 303 (27), 275 (84), 249 (27), 210 (26), 171 (86), 121 (78), 93 (35), 77 (22), 65 (76). Anal. Calcd for $C_{18}H_{14}N_4O_5$ (366.34); C, 59.02; H, 3.85; N, 15.29%. Found: C, 59.15; H, 3.82; N, 15.06%.

5-(2-Hydroxybenzoyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (13).

A mixture of compound **2** (0.67, 3 mmol) in 95% EtOH (25 mL) containing one drop of piperidine was heated under reflux for 2 h. The solid obtained after cooling was filtered off and crystallized from EtOH to give compound **13** as white crystals, yield (0.31 g, 43%), mp 270 °C (lit., mp 266−267 °C).[25] IR (KBr, cm^{-1}): 3182, 3078 (OH, NH), 3002 ($CH_{arom.}$), 2228 (C≡N), 1688 ($C=O_{cyclic\ amide}$), 1641 ($C=O_{benzoyl}$), 1617 (C=C). ^{1}H NMR (DMSO-d_6, δ): 6.92−7.98 (m, 2H, Ar-H), 7.35 (d, 1H, Ar-H, J = 6.0 Hz), 7.42 (t, 1H, Ar-H, J = 7.5 Hz), 8.05 (s, 1H, H-$4_{pyridine}$), 8.42 (s, 1H, H-$6_{pyridine}$), 10.33 (bs, 1H, NH exchangeable with D_2O), 13.10 (bs, 1H, OH exchangeable with D_2O).

5-Amino-3-[(2-hydroxyphenyl)-1*H*-pyrazol-4-yl]-1*H*-pyrazole-4-carbonitrile (14).

A mixture of compound **2** (0.67 g, 3 mmol) and hydrazine hydrate (0.15 mL, 3 mmol) in absolute EtOH (25 mL) was heated under reflux for 30 min. The solid obtained during heating was filtered off and crystallized from DMF/EtOH to give compound **14** as yellow crystals, yield (0.32 g, 60%), mp 255 °C. IR (KBr, cm^{-1}): 3335 (br, NH_2, 2NH, OH), 2221 (C≡N), 1624 (C=N), 1602 (C=C). ^{1}HNMR (DMSO-d_6, δ): 6.95-6.99 (m, 3H, 3Ar-H), 7.31 (d, 1H, Ar-H, J = 8.7 Hz), 7.47 (bs, 2H, NH_2 exchangeable with D_2O), 7.64 (s, 1H, H-$5_{pyrazole}$), 10.20 (bs, 3H, 2NH and OH exchangeable with D_2O). M/z (*I* %): 241 (M-CN,

46), 93 (39), 83 (54), 64 (100). Anal. Calcd for $C_{13}H_{10}N_6O$ (266.26); C, 58.64; H, 3.76; N, 31.56%. Found: C, 58.33; H, 3.54; N, 31.67%.

5-Amino-7-(4-oxo-4*H*-chromen-3-yl)-2,3-dihydro-1*H*-1,4-diazepine-6-carbonitrile (15).

A mixture of compound **2** (0.67 g, 3 mmol) and ethylenediamine (0.2 mL, 3 mmol), in absolute EtOH (20 mL) was heated under reflux for 2 h. After cooling, the solid obtained was filtered off and crystallized from DMF/H_2O to give compound **15** as yellow crystals, yield (0.47 g, 70%), mp 283 °C. IR (KBr, cm^{-1}): 3324 (NH_2, NH), 3050 ($CH_{arom.}$), 2929, 2867 ($CH_{aliph.}$), 2212 (C≡N), 1645 ($C{=}O_{\gamma\text{-pyrone}}$), 1601 (C=N), 1585 (C=C). ^{1}H NMR (DMSO-d_6, δ): 3.83 (s, 4H, $2CH_2$), 5.83 (bs, 2H, NH_2 exchangeable with D_2O), 6.91−6.99 (m, 2H, Ar-H), 7.18−7.46 (m, 1H, Ar-H), 8.06 (d, 1H, H-5), 8.88 (s, 1H, H-2), 9.91 (bs, 1H, NH exchangeable with D_2O). M/z (*I* %): 279 (M-1, 24), 182 (23), 140 (29), 94 (41), 64 (82), 55 (100). Anal. Calcd for $C_{15}H_{12}N_4O_2$ (280.29); C, 64.28; H, 4.32; N, 19.99%. Found: C, 64.68; H, 4.60; N, 19.32%.

4-Amino-2-(4-oxo-4*H*-chromen-3-yl)-1*H*-1,5-benzodiazepine-3-carbonitrile (16).

A mixture of compound **2** (0.67 g, 3 mmol) and *o*-phenylendiamine (0.32 g, 3 mmol) in absolute EtOH (25 mL) was heated under reflux for 2 h. The solid obtained during heating was filtered off and crystallized from DMF/EtOH to give compound **16** as yellow crystals, yield (0.42 g, 63%), mp 292 °C. IR (KBr, cm^{-1}): 3319 (NH_2, NH), 3052 ($CH_{arom.}$), 2210 (C≡N), 1633 ($C{=}O_{\gamma\text{-pyrone}}$), 1615 (C=N), 1582 (C=C). ^{1}HNMR (DMSO-d_6, δ): 6.89-6.98 (m, 3H, Ar-H), 7.44-7.58 (m, 4H, Ar-H), 7.69 (bs, 2H, NH_2 exchangeable with D_2O), 7.80 (d, 1H, $H\text{-}5_{chromone}$), 8.30 (bs, 1H, NH exchangeable with D_2O), 8.75 (s, 1H, $H\text{-}2_{chromone}$). ^{13}C NMR (DMSO-d_6, δ): 71.5, 116.2, 116.7, 117.3, 119.1, 122.6, 124.3, 126.2, 127.6, 130.8, 133.2, 140.1, 146.1, 151.6, 152.8, 156.8, 183.4. M/z (*I* %): 328 (M, 88), 311 (69), 299 (63), 256 (25), 208 (100), 152 (25), 121 (63), 93 (38), 65 (75). Anal. Calcd for $C_{19}H_{12}N_4O_2$ (328.33); C, 69.51; H, 3.68; N, 17.06%. Found: C, 69.64; H, 3.33; N, 17.00%.

6-Amino-2-oxo-4-(4-oxo-4*H*-chromen-3-yl)-1,2-dihydropyridine-3,5-dicarbonitrile (17).

A mixture of compound **2** (0.44 g, 2 mmol) and cyanoacetamide (0.17 g, 2 mmol) in absolute EtOH (20 mL) containing two drops of piperidine was heated under reflux for 2 h. The yellow crystals obtained during heating was filtered off and crystallized from DMF/EtOH to give compound **17** as pale yellow crystals, yield (0.20 g, 45%), mp > 300 °C. IR (KBr, cm^{-1}): 3385, 3320, 3195 (br, NH_2, NH), 3050 ($CH_{arom.}$), 2217 ($2C{\equiv}N$), 1684 ($C{=}O_{pyridone}$), 1663 ($C{=}O_{\gamma\text{-pyrone}}$), 1622 (C= N). ^{1}HNMR (DMSO-d_6, δ): 7.51 (t, 1H, $H\text{-}6_{chromone}$, J = 7.8 Hz), 7.62 (d, 1H, $H\text{-}8_{chromone}$, J = 8.7 Hz), 7.77 (t, 1H, $H\text{-}7_{chromone}$, J = 7.8 Hz), 7.88 (d, 1H, $H\text{-}5_{chromone}$, J = 8.4 Hz), 8.25 (s, 1H, NH), 8.56 (s, 1H, NH), 8.97 (s, 1H, NH), 9.26 (s, 1H, $H\text{-}2_{chromone}$). M/z (*I* %): 304 (M^+, 13), 288 (10), 275 (9), 262 (10), 250 (14), 235 (10), 214 (15), 185 (9), 172 (13), 131 (12), 121 (13), 94 (11), 80 (100), 77 (9), 64 (42). Anal. Calcd for $C_{16}H_8N_4O_3$ (304.27); C, 63.16; H, 2.65; N, 18.41%. Found: C, 62.89; H, 2.51; N, 18.16%.

1,6-Diamino-2-oxo-4-(4-oxo-4*H*-chromen-3-yl)-1,2-dihydropyridine-3,5-dicarbonitrile (18).

A mixture of compound **2** (0.44 g, 2 mmol) and cyanoacetohydrazide, (0.2 g, 2 mmol), in absolute EtOH (50 mL) containing two drops of piperidine, was heated under reflux for 30 min. The pale yellow precipitate obtained during heating was filtered off and crystallized from DMF/MeOH to give compound **18** as yellow crystals, yield (0.27 g, 61%), mp 289 °C. IR (KBr, cm^{-1}): 3183, 3085 ($2NH_2$), 2999 ($CH_{arom.}$), 2225 (2C≡N), 1689 ($C=O_{pyridone}$), 1644 ($C=O_{\gamma\text{-pyrone}}$), 1624 (C=C). ^{1}HNMR (DMSO-d_6, δ): 4.55 (s, 2H, *N*-NH_2 exchangeable with D_2O), 6.98-7.04 (d, 2H, Ar-H), 7.38-7.58 (m, 2H, Ar-H), 8.80 (s, 2H, *C*-NH_2 exchangeable with D_2O), 9.38 (s, 1H, H-$2_{chromone}$). M/z (*I* %): 319 (M^+, 17), 304 (18), 273 (18), 225 (19), 217 (17), 167 (20), 144 (17), 115 (16), 92 (17), 77 (12), 65 (100). Anal. Calcd for $C_{16}H_9N_5O_3$ (319.28): C, 60.19; H, 2.84; N, 21.93%. Found: C, 60.23; H, 2.86; N, 21.74%.

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